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Association of *in utero* magnesium exposure and spontaneous intestinal perforations in extremely low birth weight infants

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Abstract

Objective—Determine whether antenatal exposure to magnesium is associated with spontaneous intestinal perforation in extremely low birth weight infants (≤1000 g).

Study Design—We identified all extremely low birth weight infants admitted to one of 323 neonatal intensive care units from 2007 to 2013. We used multivariable conditional logistic regression to compare outcomes in the first 21 days after birth between infants exposed and unexposed to magnesium *in utero*.

Results—Of the 28,035 infants, 11,789 (42%) were exposed to *antenatal* magnesium. There was no difference in the risk of spontaneous intestinal perforation, odds ratio=1.08 (95% confidence interval; 0.91–1.29), between infants exposed and unexposed to antenatal magnesium. Mortality in the first 21 days after birth was lower in the magnesium exposed infants, odds ratio=0.76 (0.70–0.83).

Conclusion—Antenatal magnesium exposure in extremely low birth weight infants was not associated with increased risk of spontaneous intestinal perforation.

Keywords

neonate; safety; antenatal

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Conflict of Interest

All other authors reported no conflicts of interest.

INTRODUCTION

Antenatal magnesium (AM) has several uses including seizure prophylaxis for mothers with preeclampsia, tocolysis, and, most recently, neuroprophylaxis for premature infants.(1–7) AM is beneficial in stopping the progression from preeclampsia to eclampsia.(7) The evidence is inconclusive in regards to its use for tocolysis, with a systematic review concluding no benefit in preventing premature birth.(6) Over the past several years, there has been a growing body of evidence to suggest that AM is effective in improving neurologic outcomes in premature infants.(3, 5, 8)

Magnesium acts as an enzyme cofactor and is involved in the function of the ATPase sodium-potassium pump. Magnesium is also a central nervous system depressant and inhibits peripheral neuromuscular transmissions, impairing intestinal tract motility and function. Data are mixed on the effect of AM on the gastrointestinal system. A delay in first stool has been observed in premature infants exposed to AM for maternal preeclampsia in some studies(9), though not in others.(10–12) AM has not been shown to affect neonatal intestinal blood flow,(13) meconium plug syndrome,(14) or necrotizing enterocolitis (NEC).(3, 5) However, the relationship between magnesium and spontaneous intestinal perforations (SIPs) has not been widely investigated.

At our institution, we observed an increased risk of SIPs in premature infants following the initiation of AM administration for neuroprophylaxis.(15) Here, we evaluated a large multicenter cohort to determine if AM exposure was associated with SIP or death in extremely low birth weight infants (ELBW, ≤1000 g birth weight).

SUBJECTS AND METHODS

Study Design and Setting

We used a database derived from electronic medical records generated by clinicians on all infants cared for by the Pediatrix Medical Group in 323 neonatal intensive care units (NICUs) in North America. Data on multiple aspects of care were entered into a shared electronic medical record to generate admission, daily progress notes, and discharge summaries. Information regarding maternal history, demographics, medications, laboratory results, diagnoses, and procedures was then transferred to the Pediatrix Clinical Data Warehouse for quality improvement and research purposes. [9] We included 28,035 ELBW infants discharged between 1997 and 2013. We excluded outborn infants and those with severe congenital anomalies. The study was approved by the Duke University Institutional Review Board.

Definitions and Participants

We defined AM exposure as an infant with AM exposure for any reason prior to delivery. The primary outcome was defined as the occurrence of a SIP in the first 21 days after birth. Secondary outcomes included the diagnoses of surgical or medical NEC, death, grade 3 or 4 intraventricular hemorrhage (IVH), and the combined outcome of SIP, NEC, or death in the first 21 days after birth. We defined postnatal exposure to hydrocortisone or indomethacin/ibuprofen as either exposure prior to an outcome, or exposure in the first 21 days after birth

if an infant did not experience an outcome. Given that the diagnoses of SIP and surgical NEC sometimes overlap, an infant who was diagnosed with both had the episode classified as surgical NEC. Likewise, if an infant had both medical NEC and surgical NEC diagnoses, the episode was classified as surgical NEC.

Statistical Methods

The unit of observation for this analysis was the infant. We compared demographic distributions among infants with and without AM exposure using Fisher's exact test. We used conditional logistic regression conditioned on site to account for the clustered nature of the data to evaluate the association between AM exposure and the outcomes of SIP, NEC, death, IVH or the combined outcome of SIP, NEC or death. All models were adjusted for gestational age at birth, multiple gestation, antenatal steroid exposure, antenatal antibiotic exposure, prolonged rupture of membranes, small for gestational age, gender, postnatal hydrocortisone exposure, postnatal indomethacin exposure, and year. STATA 14 (College Station, TX) was used to perform the statistical analysis. For inquiries into the availability of the code please contact the corresponding author. A $p<0.05$ was considered statistically significant for all tests.

RESULTS

Of 28,035 ELBW infants admitted to the NICU during the study period, 11,789 (42%) were exposed to AM (Table 1). Demographic characteristics were similar between those exposed and unexposed to AM, except for the administration of antenatal steroids (94% in AM group versus 70% in unexposed group) and antenatal antibiotics (55% in AM group versus 35% unexposed group [Table 1]). The median birth weight for infants exposed and not exposed to AM was 775 g (25^{th}, 75^{th}%tile; 650, 890) and 767 g (630, 890). The median gestational age for infants exposed to AM was 26 weeks (25^{th}, 75^{th}%tile; 25, 27) and not exposed to AM was 26 weeks (24, 27). Use of AM increased over time; 28% of ELBW infants were exposed to AM in 2007, and 56% of ELBW infants were exposed in 2013.

There were a total of 710 infants with SIPs, 340/11,789 (2.9 %) in the AM exposed and 370/16,246 (2.3%) in the unexposed group. Of the 710 infants with SIPs, 73% were ≤ 26 weeks gestational age. There was no significant difference in the adjusted odds of SIPs between infants exposed and unexposed to AM, odds ratio =1.08 (95% confidence interval; 0.91–1.29). Given recent concerns about misclassification of subjects with both SIP and surgical NEC diagnoses, we performed an additional analysis where all infants with both diagnoses were classified as a case of SIP.(16) This yielded similar results with an odds ratio of 1.05 (95% confidence interval; 0.89–1.50). Results were similar when adjusted analyses was repeated after excluding infants with unknown survival status at hospital discharge, odds ratio=0.98 (0.80–1.19). There were a total of 3887 infant deaths in the first 21 days after birth and infants exposed to AM had lower mortality, odds ratio=0.76 (0.70–0.83) (Table 2). There was no difference in medical NEC, surgical NEC, or IVH between the 2 groups.

DISCUSSION

Current obstetrical practice is to use AM for seizure prophylaxis in preeclampsia, tocolysis, and most recently, neuroprophylaxis for mothers at imminent risk of premature delivery. With this new indication, increasing numbers of premature infants are exposed to AM. At our institution we noticed an increase in SIP in ELBW infants after the initiation of magnesium for neuroprophylaxis, a complication that, to our knowledge, has not been described in the literature.(15) In the present study, 11,789 of 28,035 (42%) ELBW infants were exposed to AM. We did not observe an association between AM exposure and SIPs in ELBW infants.

SIP is recognized as an entity separate from NEC. The pathophysiology of SIP is not fully understood; possible causes include decreased gastrointestinal perfusion, thinning of the intestinal lining, and administration of certain medications such as steroids or indomethacin.(17) SIP is most common in ELBW infants, with an incidence ranging from 2.2% to 8.4%.(18–20) At our institution, we examined the risk of SIP before and after initiation of routine AM neuroprophylaxis protocol, after noting a cluster of perforations among our ELBW infants. Prior to the AM neuroprophylaxis protocol, 51% of the ELBW infants were exposed to AM compared to 78% after its implementation. The incidence of SIPs in ELBWs increased from 12% to 30% (p=0.09) with the implementation of AM use for neuroprophylaxis.(15) This observation led us to conduct this multicenter retrospective study evaluating the association between SIP and AM exposure across the Pediatrix network. The incidence of SIP in this cohort (2.5%) was on the lower side of the range reported in the literature (18–20) and we found no difference in the adjusted risk of SIP between infants exposed and unexposed. Uncontrolled or unknown causes of SIP may explain the different results between these cohorts.

Unlike SIP, NEC has been a commonly reported outcome in trials investigating the use of AM magnesium for neuroprophylaxis. Several randomized control trials showed no significant difference in the incidence of NEC between placebo and AM treatment groups.(3, 5, 8) Our findings are consistent with these previous studies, showing no increase in NEC. However, when interpreting these data, there is the possibility that some infants with NEC were transferred to other centers for more specialized or surgical care prior to their NEC diagnosis, which may decrease the total number of NEC cases in this cohort.

IVH may increase the risk of cerebral palsy,(21–24) which could influence the neuroprotective effect of magnesium. Previous reports showed no difference in IVH in infants exposed to AM versus those unexposed.(3, 5, 8, 25, 26) This study supports the previous literature with no significant difference in IVH between the two groups.

The initial randomized controlled study to evaluate the use of AM to decrease cerebral palsy was stopped prior to completion due to an increase in total pediatric deaths in the group exposed to high doses of magnesium (greater than 50 grams) (risk difference 15.2%; 95% CI 4.4–26.0, p=0.01).(27) However, none of the 3 completed randomized controlled studies had a significant increase in deaths.(3, 5, 8) It should be noted that these 4 studies all used different magnesium doses, with the study that ended prematurely using some of the highest

doses.(3, 5, 8, 27) In our study, we saw a decrease in death in the first 21 days after birth in the exposure group (5.7% versus 8.2%, $p<0.05$). This finding should be interpreted with caution, as we do not have any data on dosing, timing, or indication for AM treatment. Additionally, 9.9% of our cohort had missing death data. Further investigation is required to better define the relationship between AM exposure, death, and dosing.

This is the largest study to report on the use of AM in ELBW infants, and the only one to our knowledge to examine the association of AM with SIPs. Strengths of this study include population diversity from academic and community institutions, ability to adjust for multiple potential confounders, and a contemporary study period. Our results are generalizable to young infants admitted to a NICU following AM exposure.

This study has several limitations including its retrospective design, the inability to determine the indication for AM administration, the total dose administered, magnesium levels of the mother and infants, and timing of the magnesium administration in relation to birth. There may be differences in outcomes depending on indication. For example, infants born to mothers receiving AM for seizure prophylaxis often have placental insufficiency and growth retardation. This may alter their risk of SIP compared to infants exposed to AM for neuroprophylaxis. Another limitation is the lack of data once an infant is transferred to another hospital outside of the Pediatrix network. Outcomes such as SIP, NEC, or death may be missed on these infants. Therefore, the results need to be interpreted with caution.

In this large multicenter study we observed no significant difference in SIP, NEC, or IVH between those infants exposed to AM and those unexposed. We did report a significant decrease in death in the first 21 days after birth, though that data had a large amount of missing data. Future investigations should prospectively investigate the role of AM on SIPs, and examine the role of AM dosing on infant outcomes.

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Abbreviations

AM	Antenatal magnesium
ELBW	Extremely low birth weight

IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
SIP	Spontaneous intestinal perforation

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Table 1

Demographics

	Magnesium exposed(%) N=11,789	**Unexposed (%) N=16,246**
Gestation (weeks)		
< 26	5165 (44%)	7346 (45%)
26–28	5400 (46%)	6781 (42%)
≥ 29	1224 (10%)	2109 (13%)
Birth weight (g)		
≤ 750	5374 (46%)	7683 (47%)
751–1000	6415 (54%)	8563 (53%)
Race/Ethnicity		
White	4902 (42%)	6442 (40%)
Black	3892 (33%)	5187 (32%)
Hispanic	2011 (17%)	3151 (19%)
Other	647 (5%)	845 (5%)
Multiple gestation	2072 (18%)	2576 (16%)
Male	5802 (49%)	8080 (50%)
PROM	1579 (13%)	2467 (15%)
Antenatal steroids	11,098 (94%)	11,336 (70%)
Antenatal antibiotics	6451 (55%)	5697 (35%)
Postnatal hydrocortisone	888 (8%)	1374 (8%)
Postnatal indomethacin	2369 (20%)	3045 (19%)

PROM: prolonged rupture of membranes

Table 2

Outcomes in the magnesium exposed and unexposed group *p<0.05

	Magnesium N=11,789	No Magnesium N=16,246	Adjusted OR** (95% CI)
SIP	340 (2.9%)	370 (2.3%)	1.08 (0.91, 1.29)
Death	1338 (11.4%)	2549 (15.7%)	0.76 (0.70, 0.83)*
Surgical NEC	143 (1.2%)	253 (1.6%)	0.84 (0.66, 1.05)
Medical NEC	191 (1.6%)	270 (1.7%)	1.11 (0.89, 1.37)
Death, NEC, or SIP	1882 (16.0%)	3248 (20.0%)	0.84 (0.77, 0.90)*
IVH (Grade 3 or 4)	1219 (10.3%)	1889 (11.6%)	0.97 (0.88, 1.06)

CI: confidence interval; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; SIP: Spontaneous intestinal perforation; OR: odds ratio

** adjusted for site, gestational age at birth, multiple gestation, antenatal steroid exposure, antenatal antibiotic exposure, prolonged rupture of membranes, small for gestational age, sex, discharge year, postnatal hydrocortisone exposure, and postnatal indomethacin exposure